PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The clustering of cardiovascular disease risk factors and their impacts on annual medical expenditure in Japan: community-based cost analysis using Gamma regression models
AUTHORS	Murakami, Yoshitaka ; Okamura, Tomonori; Nakamura, Koshi; Miura, katsuyuki; Ueshima, Hirotsugu

VERSION 1 - REVIEW

REVIEWER	Toshimi Sairenchi, PhD Associate professor Department of Public Health, Dokkyo Medical University School of Medicine, I have no competing interest to declare.
REVIEW RETURNED	07-Nov-2012

GENERAL COMMENTS	The authors report results from 5 years follow-up of 31,119 NIH beneficiaries in Shiga, Japan in which they examined the age- and sex-specific association between CVD risk factors and total medical expenditures. They found that the annual medical expenditure increased as the number of CVD risk factors in all age and sex groups. In addition, they also found that the excess medical expenditure were larger among the group with one or two CVD risk factors while cost ratios were largest among the group with three or four CVD risk factors. The findings are very interesting. I outline some areas for further detail or clarification below: Minor Points 1. As the authors mentioned, the medical treatment status was not considered in the analysis. Patients with medication might have been treated as participants with no CVD risk factor. That might have led underestimate. This point should be stated in more detail in Discussion. In addition, it might be better to do a sub-analysis in which the participants with medical expenses data in the first year were excluded if possible. 2. The signs of inequality '>' in Abstract are '≥'. 3. Using Gamma regression to estimate the mean annual medical expenditure should be stated in Fugure legends.

REVIEWER	Hideki Hashimoto, MD, DPH Professor in health economics and epidemiology research. University of Tokyo, School of Public Health, Japan. I declare no interests of conflict and competing interests for this

	study.
REVIEW RETURNED	16-Nov-2012

THE STUDY	The authors analyzed a large claim data of the National Health Insurance in a Japanese prefecture to identify the medical expenditure related to conventional risk factors for cardiovascular diseases, namely hypertension, diabetes, hypercholesterolemia and smoking. As I understand, the authors concluded that the larger the number of coexisting risk factors was, the larger the medical expenditure became during observed six years. I am confused by the author's argument on what they call "excess medical expenditure". If the beneficiaries with "risk factors" were medically treated for these conditions, it is simply obvious that these beneficiaries spent more medical resources because of these "comorbid" conditions. Do the authors estimate medical expenditure specifically for cardiovascular conditions, excluding treatment cost for hypertension, diabetes, hypercholesterolemia and smoking cessation? If so, their argument makes sense. Otherwise, I do not think the analysis adds anything to the literature. Another concern is on their choice of analytic model. The authors simply took an average expenditure per year for each of six years, and relied on GEE with gamma link function, as I understand. If they hypothesized that risk factors affect the incidence of cardiovascular conditions and their severity, then one could expect the disparity in expenditure by risk factors would be widened over time. Then, the authors should have tested the interaction between time and the number of risk factors. The authors should provide a rationale why they did not do so. As the authors already recognized, the utilization is often distributed in zero-truncated manner. Thus, in health economics literature, the utilization is often treated in so-called two-part model, or the probability of utilization and the frequency / amount of utilization given the utilization happens. It is because the factors affecting the probability and amount of utilization would be different. For example, two persons spent the same average utilization per year, but one used frequent and cheap services while the other used one time expensive service. Two part model could better identify the pattern of use as above, and could tell whether the patient with risk factors used frequent visits or costly services, or both. Other choices to treat utilization probability and amount might be Tobit regression and negative binominal regression. Again the authors could have presented a better rationale why they did not use these options, and simply relied on "average utilization".

VERSION 1 – AUTHOR RESPONSE

Reply to Dr. Sairenchi's comments;

1. As the authors mentioned, the medical treatment status was not considered in the analysis. Patients with medication might have been treated as participants with no CVD risk factor. That might have led underestimate. This point should be stated in more detail in Discussion. In addition, it might be better to do a sub-analysis in which the participants with medical expenses data in the first year were excluded if possible.

We agreed with your opinion that the medical treatment status is the key factor for a medical

expenditure increase in the population. According to your advice, we added some sentences for the medical treatment effect on the medical expenditure in Discussion section as follows;
Line 10-16, page13
First, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable in this study. It is true that the medical treatment status and the clinical conditions are key elements of increasing medical expenditure. Our reference group contained both the non-prescribed (healthy population) and the prescribed. This might overestimate the “referent” mean medical expenditure. From this viewpoint, the relative measures (cost ratios) of CVD risk factors might be underestimated in this study.

According to your advice, we conducted the analysis of the participants whose medical expenses in the first year were excluded. The result of figure 1 was quite similar to that in the original Figure1, except for the young men with no risk factor, whose population was quite small in this sensitivity analysis.

2. The signs of inequality ‘>’ in Abstract are ‘≥’.
Thank you for pointing out our mistakes. We have made the correction according to your advice.

3. Using Gamma regression to estimate the mean annual medical expenditure should be stated in Figure legends.
Thank you for your comments. We included the sentences in Figure 1 and Figure 2.

Reply to Dr. Hashimoto’s comments;

1. I am confused by the author’s argument on what they call “excess medical expenditure”. If the beneficiaries with “risk factors” were medically treated for these conditions, it is simply obvious that these beneficiaries spent more medical resources because of these “comorbid” conditions. Do the authors estimate medical expenditure specifically for cardiovascular conditions, excluding treatment cost for hypertension, diabetes, hypercholesterolemia and smoking cessation? If so, their argument makes sense. Otherwise, I do not think the analysis adds anything to the literature.

The aim of this paper is the quantitative assessment of the risk factors’ effects on the medical expenditure. Though we knew that the “comorbid” conditions of risk factors increased the medical expenditure of an individual, it is not obvious about their impacts on the medical expenditure in a population. This investigation could only achieve using both the medical expenditure and their distribution on the study population, like Figure 2. We also see that little is known about their quantitative impacts of risk factors on medical expenditure, especially using the absolute measures in the analysis, like Figure 1. We included some sentences to make our study aims clearer in the Abstract and the Introduction;

Line 4-6, page 2
The age-specific quantitative assessment of the medical expenditure, especially focused on the elderly, is thus indispensable for formulating public health policy given the extent of the ageing population in developed countries.

Line 14-16, page 5
The present study thus conducted the age- and sex-specific quantitative assessments of total medical expenditure and examines how the clustering of CVD risk factors affects the Japanese population.

We agreed that the medical treatment status is the key factor for a medical expenditure increase in the population. We added some sentences about the medical treatment effect on the medical

expenditure in Discussion section as follows;

Line 10-16, page13
First, details of medical diagnoses, medical treatment status (e.g. prescriptions), clinical condition such as CVD history, and cause of mortality were unavailable in this study. It is true that the medical treatment status and the clinical conditions are key elements of increasing medical expenditure. Our reference group contained both the non-prescribed (healthy population) and the prescribed. This might overestimate the “referent” mean medical expenditure. From this viewpoint, the relative measures (cost ratios) of CVD risk factors might be underestimated in this study.

2. Another concern is on their choice of analytic model. The authors simply took an average expenditure per year for each of six years, and relied on GEE with gamma link function, as I understand. If they hypothesized that risk factors affect the incidence of cardiovascular conditions and their severity, then one could expect the disparity in expenditure by risk factors would be widened over time. Then, the authors should have tested the interaction between time and the number of risk factors. The authors should provide a rationale why they did not do so.

We actually used the average of the medical expenditure during a whole observation periods, not a single year of observation. We used GEE for adjusting the regional differences, not for considering a correlation structure among individuals. Each individual in the dataset involves his/her characteristics, risk factors and a single outcome (the average medical expenditure (per year)). In this situation, no interaction test between time and the number of risk factors was possible in the model.
The observation period of each participant differed and this time period depended on their membership status of their health insurance. To make a fair comparison of the medical expenditure among groups, we used the mean medical expenditure, which was calculated by summing up all medical expenditure throughout the observation periods and divided by the total observation periods of months. Finally, this monthly-based measures are multiplied twelve to transform a mean ”annual” medical expenditure.
We agreed that this term “mean annual medical expenditure” led you confusing, so we changed all this term to “mean medical expenditure (per year)” in our text. We also changed our explanation to write the detail as follows;
Line 17, page 6 to line 2, page 7.
For the economic evaluation, we used a mean medical expenditure (per year), which was calculated by summing all medical expenditure throughout the observation periods and divided by the total observation periods of months. This monthly-based measure is multiplied twelve to transform a mean medical expenditure (per year).

3. As the authors already recognized, the utilization is often distributed in zero-truncated manner. Thus, in health economics literature, the utilization is often treated in so-called two-part model, or the probability of utilization and the frequency / amount of utilization given the utilization happens. It is because the factors affecting the probability and amount of utilization would be different. For example, two persons spent the same average utilization per year, but one used frequent and cheap services while the other used one time expensive service. Two part model could better identify the pattern of use as above, and could tell whether the patient with risk factors used frequent visits or costly services, or both. Other choices to treat utilization probability and amount might be Tobit regression and negative binominal regression. Again the authors could have presented a better rationale why they did not use these options, and simply relied on “average utilization”.

In the current health economic literature 1) and the textbook 2), the Gamma regression model are applied in cost data analysis. The guideline from the International Society of Pharmacoeconomics and Outcome Research (ISPOR) recommended using this statistical model in the cost data analysis 3).

The cost data often show a skewed distribution, which violated the equidispersion property of mean and variance. In this case, a negative-binomial regression is an option, but a Gamma regression is most suitable statistical model, which assumed extra-variation (overdispersion) of the outcome, such as the zero-inflated data. The two-parts models including Tobit regression and hurdle regression are attractive idea to deal with “the zero value”, especially the substantial numbers of zero are found in the distribution. 2)

1) Hill SC, Miller GE. Health expenditure estimation and functional form: applications of the generalized gamma and extended estimating equations models. Health Econ. 2010;19:608-27.
2) Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. New York: Oxford University Press, 2007.
3) Ramsey S, Willke R, Briggs A et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health. 2005;8:521–33.

We decided to apply the Gamma regression model to analyze the data because the number of zero values are not so substantial in our study. To make this point clearer, and show the Discussion, we included some sentences in the manuscript.

Line 5, Page 12.
The guideline from the International Society of Pharmacoeconomics and Outcome Research (ISPOR) recommended using this statistical model in the cost data analysis 13). The cost data often show a skewed distribution, which violated the equidispersion property of mean and variance. In a case with a certain proportion of zeros, a Gamma regression is most suitable statistical model, which assumed the extra-variation (overdispersion) of the outcome.

VERSION 2 – REVIEW

REVIEWER	Hideki Hashimoto, MD, DPH. the University of Tokyo School of Public Health, Tokyo, Japan. No conflicts of interests declared.
REVIEW RETURNED	02-Jan-2013

THE STUDY	Research question could have been stated in clearer and more specific manner. "average utilization per person" may not be an appropriate indicator to compare cost b/w treatment and control groups.
RESULTS & CONCLUSIONS	The comparison of treatment vs. control group may be biased due to cost related to end-of-life treatment cost.
GENERAL COMMENTS	The authors provided in this revision and associated letter more details on their motives, purposes, and rationale of analytic strategies they chose. However, the authors still need to more clearly state their purpose of the study, and could reconsider the analytic mode for more precise comparison and less biased estimation for the cost impact of cardiovascular risk factors. 1. In response to my last comment, the authors replaced the phrase “excessive medical expenditure” with “age-specific quantitative assessment of the medical expenditure”, though this revised phrase still fails to specifically express their message. As I understand, what the authors intended to do was to estimate the age-specific proportion and distribution of medial expenditure attributable to cardiovascular conditions and related risk factors specifically focusing on the elderly population in

	Japan. If so, they should describe more specifically what they intended to do. I do admit that with figures 1 and 2, the authors brought an important policy message that the condition with a fewer risk factors was mildly costly, but more prevalent, resulting in a largest impact as a whole. 2. If my understanding above is correct, this is not "cost minimization analysis" at all. Instead, it is cost analysis or estimation of cost. 3. I am still confused regarding their unit of analysis. As I read the response letter from the authors, they took monthly average throughout the observed period for each person, then multiplied it by 12 to estimate yearly average per person. This may be problematic in two holds. First, and for most is that they lost information on time and change trend by simply taking average throughout the observed period. Since the original dataset the authors hold is derived from monthly claim information, and should include monthly utilization information per person, the loss of the information is a serious waste and can be a source of estimation bias. As I pointed out in the last comment, if the authors used person-month as a unit of analysis, and included time information in their analysis, they could have been tested whether the existence of risk factors increased expenditure over time (which should imply a higher incidence of conditions requiring costly treatment among the treatment group, e.g. coronary intervention for acute coronary syndrome and hemo-dialysis for renal failure), or the expenditure was somewhat constant over time (which should imply treatment of risk factor conditions per se makes the difference). The trend analysis could have brought more specific lessons for policy making to prevent high cost situation incurred by risk factors. Related to the first problem is the treatment of cost of end-of-life treatment. As a rich accumulation of economic literature revealed, the medical expenditure is often intensively used in the last few months before death. Thus, the estimated "excess" cost among those with risk factors could be simply attributed to their premature death, though those survived will spend similar or more medical expenditure in future for other medical conditions, e.g. cancer and dementia. If such was the case, the higher cost among those with cardiovascular factors was spuriously estimated because the observation period was not enough among their control without risk factors who will die later. Again, simply taking average throughout the observed period could not discriminate the situation above, unless dead cases were excluded from the analysis. To the contrary, time trend analysis with inclusion of "time to death" as a covariant could have brought more detailed information and precise comparison between those with risk factors and their healthier control. For the analysis above, two-part model would be a better choice as I mentioned in the last comment.

VERSION 2 – AUTHOR RESPONSE

Reply to the comments from Professor Hashimoto;

1. In response to my last comment, the authors replaced the phrase “excessive medical expenditure” with “age-specific quantitative assessment of the medical expenditure”, though this revised phrase still fails to specifically express their message. As I understand, what the authors intended to do was to estimate the age-specific proportion and distribution of medial expenditure attributable to cardiovascular conditions and related risk factors specifically focusing on the elderly population in Japan. If so, they should describe more specifically what they intended to do. I do admit that with figures 1 and 2, the authors brought an important policy message that the condition with a fewer risk factors was mildly costly, but more prevalent, resulting in a largest impact as a whole.

Thank you for your comments. According to your advice, we changed some sentences in our manuscript to clarify our study objectives; the investigation of the age-specific proportion and distribution of medial expenditure attributable to cardiovascular conditions and related risk factors.

Line 4, page 2,
Objective
The age-specific proportion and distribution of medical expenditure attributable to CVD risk factors, especially focused on the elderly, is thus indispensable for formulating public health policy given the extent of the ageing population in developed countries.

Line 4, Page 6,
Conclusion The age-specific proportion and distribution of medical expenditure attributable to CVD risk factors showed that a high-risk approach for the elderly and a population approach for the majority are both necessary to reduce total medical expenditure in Japan.

Line 13, Page 5,
The present study examined the age- and sex-specific proportion and distribution of medical expenditure attributable for the number of CVD risk factors in the Japanese population.

2. If my understanding above is correct, this is not “cost minimization analysis” at all. Instead, it is cost analysis or estimation of cost.

Thank you for your suggestion. According to your advice, we changed all ‘cost minimization analysis’ into ‘cost analysis’ in our manuscript.

3. I am still confused regarding their unit of analysis. As I read the response letter from the authors, they took monthly average throughout the observed period for each person, then multiplied it by 12 to estimate yearly average per person. This may be problematic in two holds.
First, and for most is that they lost information on time and change trend by simply taking average throughout the observed period. Since the original dataset the authors hold is derived from monthly claim information, and should include monthly utilization information per person, the loss of the information is a serious waste and can be a source of estimation bias. As I pointed out in the last comment, if the authors used person-month as a unit of analysis, and included time information in their analysis, they could have been tested whether the existence of risk factors increased expenditure over time (which should imply a higher incidence of conditions requiring costly treatment among the treatment group, e.g. coronary intervention for acute coronary syndrome and hemo-

dialysis for renal failure), or the expenditure was somewhat constant over time (which should imply treatment of risk factor conditions per se makes the difference). The trend analysis could have brought more specific lessons for policy making to prevent high cost situation incurred by risk factors. Related to the first problem is the treatment of cost of end-of-life treatment. As a rich accumulation of economic literature revealed, the medical expenditure is often intensively used in the last few months before death. Thus, the estimated "excess" cost among those with risk factors could be simply attributed to their premature death, though those survived will spend similar or more medical expenditure in future for other medical conditions, e.g. cancer and dementia. If such was the case, the higher cost among those with cardiovascular factors was spuriously estimated because the observation period was not enough among their control without risk factors who will die later. Again, simply taking average throughout the observed period could not discriminate the situation above, unless dead cases were excluded from the analysis. To the contrary, time trend analysis with inclusion of "time to death" as a covariant could have brought more detailed information and precise comparison between those with risk factors and their healthier control. For the analysis above, two-part model would be a better choice as I mentioned in the last comment.

Trend analyses are frequently conducted in Econometrics, even it is a relatively short period of time (i.e. one year or so). We were concerned that the six year of observation was not long enough for dealing with health issues in a trend analysis. Aging, deterioration, disease progression all take time and a trend analysis of these kinds also need more time for observation periods. We already mentioned this point in the limitation (line 11, page 13).
Monthly medical expenditure within individual has a serious problem; this value substantially fluctuated because most monthly expenditure showed zero in their time series. This 'substantial zeros' problem could make the results unstable and this would affect the 'overloads' estimation. In contrast, the mean medical expenditure for each individual is a stable estimate, which is suitable for the outcome variable in the statistical model. The purpose of our study is the age-specific quantitative assessment of the medical expenditure using statistical model. We thought that the 'overloads' is the important measure to examine in our manuscript. This measure was defined using the mean medical expenditure, which represented (summarized) the expenditure of an individual during a follow-up period.
We admitted the reviewer's comments that our results would be biased when we do not account for the observation periods of an individual. This typically happens when we included the patients with an end-of-life treatment in the analysis. It is also true that some diversities of follow-up period among individuals could induce a trend effect and that cause bias. To avoid this bias, we restricted the participants who have not censored during the study periods (six years) and re-analyzed. In this analysis, all participants in this dataset followed up for 6 years (no trend effect) and were alive during the follow-up period (a patient with an end-of-life treatment is negligible). The numbers and figures of the results were slightly changed but the conclusion remained the same.
According to the change of the dataset, we revised all table and figures, some words and numbers in our manuscript.

VERSION 3 - REVIEW

REVIEWER	Hideki Hashimoto, MD DPH Professor University of Tokyo School of Public Health Japan No competing interests declared
REVIEW RETURNED	16-Feb-2013

THE STUDY	Key message needs refinement.
GENERAL COMMENTS	It is a pity that two-part model was not conducted since I believe the method could have discriminated whether "overspends" happened

	due to increased visits or increased cost per visit. Yet, I admit that one-part model the authors conducted is sufficient to estimate overspends that the authors have addressed in this study. By eliminating censored observations, the revised analysis should reflect cost attributable to risk factors, with less bias due to end-of-life treatment and different observation periods. P12 Line 18 Still remains “cost minimization analysis.” Should be replaced with “cost analysis”. Following are minors and discretional; The second sentence of “Article Focus” reads odd because they did not discuss about “trend” nor any outcomes except for medical utilization. Instead, the authors may mean “The present study examined age and sex specific clustering of cardiovascular risk factors, and how it affected medical expenditure in Japanese population.” The first sentence of “Key message” should be read as “The total overspends attributable to cardiovascular risk factors is larger among non-elderly population in Japan.” The second sentence should be “Larger medical overspends were driven by the groups with one or two risk factors rather than by those with three or four, except for men aged 65 and over. The authors could find their strength in “The use of large comprehensive community-based database of health examination and medical expenditure.”

VERSION 3 – AUTHOR RESPONSE

Reply to the comments from Professor Hashimoto;

P12 Line 18
Still remains “cost minimization analysis.” Should be replaced with “cost analysis”.

Thank you helping our correction. We replaced the words that you mentioned above.

Following are minors and discretional;
The second sentence of “Article Focus” reads odd because they did not discuss about “trend” nor any outcomes except for medical utilization. Instead, the authors may mean “The present study examined age and sex specific clustering of cardiovascular risk factors, and how it affected medical expenditure in Japanese population.”

Thank you for your suggestion. According to your advice, we changed the second sentence of “Article Focus” as follows; The present study examined age and sex specific clustering of cardiovascular risk factors, and how it affected medical expenditure in the Japanese population.

The first sentence of “Key message” should be read as “The total overspends attributable to cardiovascular risk factors is larger among non-elderly population in Japan.”

Thank you for your suggestion. According to your advice, we changed the first sentence of “Key

message” as follows; The total overspends attributable to cardiovascular risk factors is larger among the non-elderly population in Japan.

The second sentence should be “Larger medical overspends were driven by the groups with one or two risk factors rather than by those with three or four, except for men aged 65 and over.

Thank you for your suggestion. According to your advice, we changed the second sentence of “Key message” as follows; Larger medical overspends were driven by the groups with one or two risk factors rather than by those with three or four, except for men aged 65 and over.

The authors could find their strength in “The use of large comprehensive community-based database of health examination and medical expenditure.”

Thank you for your suggestion. According to your advice, we changed “the strength” as follows; The use of large comprehensive community-based database of health examination and medical expenditure brought us the stratified information by sex and age.